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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/757,041	Reed et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 12, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *19 and 34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *19 and 34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed March 12, 2003 (Paper No. 13) in response to the Office Action of December 12, 2003, Paper No. 12) is acknowledged and has been entered. Previously pending claims 13-18, 20-23 have been cancelled, claims19 and 34 have been amended. Claims 19 and 34 are currently being examined.

2 The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

3. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

4. Claims 19 and 34 are rejected under 35 USC 101 because the claimed invention is not supported by a substantial utility, a well established utility, a credible utility.

The claims are drawn to a method of identifying an effective agent that alters the association of CAP-1 with a second molecule. The disclosed utility of the assay is to screen for effective agents, capable of effectively altering the association of CAP with a second molecule and by altering the association, an effective agent can increase or decrease the level of apoptosis in a cell (p. 3, lines 20-25). Since CAP-1 binds CD40, which is involved with apoptosis, an effective agent can be useful for modulating the level of apoptosis in a subject having a pathology characterized, for example, by an increased or decreased level of cell growth or cell proliferation (p. 20, lines 27-30).

The specification defines an effective agent as one that can alter the association of a Cap with a second molecule wherein the second molecule is CD40, thus an effective agent can be useful as a medicament to treat pathology characterized, in part, by abnormal cell function (p. 22, lines 12-14), an effective agent can be useful for treatment of IgE related diseases such as asthma, hay-fever, chronic sinusitis, skin rashes or allergies as well as autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, anemia, glomerulonephritis as well as decrease the proliferation of a cancer cell and can be used as a medicament to treat cancer by increasing apoptosis in a cancer cell (see page 23). However, although the specification recites a laundry list of diseases to be treated, neither the specification nor any art of record teaches a relationship of CAP-1, or an effective agent that alters the association of CAP-1 with a second molecule, to any specific diseases, establish any involvement of CAP-1, or an effective agent that alters the association of CAP-1 with a second molecule, in the etiology of any specific diseases of even demonstrate that the binding of CAP-1 to CD40 results in any functional affect upon the activity of CD40, that an effective agent that alters the association of CAP-1 with this second molecule can influence.

The asserted utility of the identified effective agent appears to be based on the finding that CAP-1 binds to CD40 intracellular domain in a yeast two-hybrid assay system (see Example I, pages 41-46), that CAP-1 binds to CD40 in a purified protein *in vitro* system, binds to CD40 in a cell lysate (see Example II, pages 47-53). Apparently, since CD40 is critical for T cell-dependent antibody responses, the

inventors hypothesize that association of CAP-1 with CD40 can affect the humoral immune response by modulating the level of production of IgG, IgA, IgE (p. 6, lines 3-5) as well as modulate apoptosis (p. 6, lines 29-35). In particular, the specification teaches that the identification of intracellular proteins that can associate with CD40 and transduce the CD40L-binding signal into the cell would provide a means to manipulate various cellular functions, thus a need exists to identify proteins that associate with CD40 and that the present invention satisfies this need (p. 3, lines 1-8). However, although the specification identifies a protein that can associate with CD40, there is no evidence presented that the association of CAP-1 with CD40 transduces the CD40L-binding signal into a cell. It is clear that further experimentation is required in order to determine whether or not the identified CAP-1 functions as suggested. This is clear especially in view of the teachings on pages 7 and 9 that although it is known that alteration in CD40 and CD40 ligand associations are involved in human diseases (p. 7, lines 24-25), the intracellular mechanism of its action remains unknown (p. 9, lines 28-30). The specification further suggests that the identification of CAP-1, which binds to the intracellular domain of CD40 provides a means to manipulate the signal transduction pathways controlled by CD40 and allows for the development of assays that are useful for identifying agents that effectively alter the association of CAP-1 with CD40 (p. 10, lines 8-15). CAP-1 was identified using the yeast two-hybrid system (p. 11, lines 17-18) and the results using such an assay **likely** (emphasis added) mirror the interactions that naturally occur in a cell (p. 11, lines 23-25). However, the unpredictability of that system and the necessity for testing this hypothesis in an *in vivo*

system is well known in the art. For example, Allen et al (TIBS, 1995 20:511) specifically teach that the most critical consideration in performing two-hybrid screens is whether true positives isolated in the system are actually representative of *in vivo* cellular interactions. "It is possible to identify interacting partners that never associate **in vivo** because they are normally expressed in different cell types, localized in distinct cellular compartments, expressed at different developmental stages etc"(page 513, col 1, last para). Further, Fields and Sternglanz (TIG, 1994, 10:287) specifically teach that interaction of the target and library-encoded proteins does not necessarily indicate that they normally interact *in vivo* since the two-hybrid system may assay an interaction between domains that are not accessible in the native protein (p. 291, col 1 last paragraph), thus the fusion process itself may alter the binding characteristics of the protein so that it will not bind *in vivo*.

Further, as drawn to the identified effective agent's usefulness as a cancer therapeutic, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example , Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the identified effective agent would function as

contemplated. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the identified effective agent would function as suggested based only on a hypotheses drawn to the known activity of CD40, especially in view of the clear admission in the specification that the mechanism of intracellular affects on CD40 was unknown at the time the invention was made. Further, as drawn to the identified effective agent's usefulness for treatment of patients with pathology associated with the immune system effects of CD40, it is well known that the art of drug discovery for autoimmune diseases is highly unpredictable. For example, as

drawn to use for patients requiring immunosuppression, Auchincloss (chapter 11 in Transplantation Immunology, Bach and Auchincloss Eds., Wiley-Liss, New York, 1995, pages 211-218) teach that many different strategies have been developed to achieve transplantation tolerance,

some of which have led to indefinite graft survival in rodents, however, none of these strategies have yet been applied to human patients in a way that allows reliable withdrawal of exogenous immunosuppression. While tolerance inducing strategies have worked well in rodents, such strategies have been much less successful even when tested in nonhuman primates and other large animals (page 211). Further, the conclusion on page 217 states that although more than a dozen different techniques to induce tolerance in rodents are now available, the fact remains that none of them has been used successfully in the clinic. Inducing transplantation tolerance in humans must therefore be very hard to do and that those reading this chapter should be wary of simple solutions to this complex problem. Further, although it is known that CD40 is involved with autoimmune diabetes and that CD40 blockade prevents autoimmune diabetes (Von Herrath, 2002, abstract, 2nd Annual Meeting of the Fed. Of Clinical Immunological Societies), it is not clear how the identified effective agent would be useful to treat diabetes since it is known in the art that by the time of clinical onset, most of the beta cells in the islets have been destroyed and the blockade of CD40 would not be expected to treat the disease, given the loss of the cells essential for producing insulin. Further, although the specification provides general teachings on dose and method of administration (p. 37, lines 12-27) there are no teachings in the

specification that establish effective doses for the identified effective agent. It is clear that to function as contemplated, the identified effective agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the site of action, interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition, the target cells must not have an alternate means of survival despite action at the proper site for the identified effective agent. The specification does not provide teachings drawn to the *in vivo* environment and variables such as biological stability, half-life or clearance from the blood which are important parameters in achieving successful therapy. The identified effective agent may be inactivated in vivo before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the identified effective agent. In addition, the identified effective agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the identified effective agent has no effect, circulation into the target area may be insufficient to carry the identified effective agent and a large enough local concentration may not be established. Finally, it is not clear how the identified effective agent would be able to treat the laundry list of immune system diseases because it does not appear that the identified effective agent would be useful to clear autoreactive T or B cells that are already in the system. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been

provided which would allow one skilled in the art to predict that the identified effective agent will function as contemplated with a reasonable expectation of success in the absence of further experimentation.

Neither the specification nor the art of record teaches whether CAP-1 is sufficient or even necessary for the modulation of CD40 function. Clearly, additional experimentation is required in order to use the effective agents to be identified with the instant method. Since additional experimentation is required the claimed invention does not have substantial utility. In addition given that other CAP-1 like molecules have been identified but that at this time Examiner is unable, despite an extensive literature search, to find any association of any of these molecules with the etiology or treatment of any specific disease, the claimed invention does not have a well established utility. It appears that the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the effective agent to be identified by the claimed method. Because the claimed invention is not supported by a substantial utility, a well-established utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

5. Claims 19 and 34 are rejected under 35 USC 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 19 and 34 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the invention.

The claims are drawn to a method of identifying an effective agent that alters the association of CAP-1 with a second molecule. The specification teaches that CAP-1 binds to CD40 (see Example I, pages 41-53) and hypothesizes that since CD40 is critical for T cell-dependent antibody responses, that the association of CAP-1 with CD40 can affect the humoral immune response by modulating the level of production of IgG, IgA, IgE (p. 6, lines 3-5) as well as modulate apoptosis (p. 6, lines 29-35). The specification further states that the identified effective agent can be useful for modulating the level of apoptosis in a subject having a pathology characterized, for example, by an increased or decreased level of cell growth or cell proliferation (p. 20, lines 27-30). The specification defines an effective agent as one that can alter the association of a Cap with a second molecule wherein the second molecule is CD40, thus an effective agent can be useful as a medicament to treat pathology characterized, in part, by abnormal cell function (p. 22, lines 12-14), including cancers and diseases of the immune system.

One cannot extrapolate the teaching of the specification to the enablement of the claims because it appears that the use contemplated for the effective agent identified by the claimed method is the *in vivo* treatment of disease. As drawn to the identified effective agent's usefulness as a cancer therapeutic, it is well known that the art of

anticancer drug discovery for cancer therapy is highly unpredictable, for example , Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the identified effective agent would function as contemplated. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress

(p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the identified effective agent would function as suggested based only on a hypotheses drawn to the known activity of CD40, especially in view of the clear admission in the specification that the mechanism of intracellular affects on CD40 was unknown at the time the invention was made. Further, as drawn to the identified effective agent's usefulness for treatment of patients with pathology associated with the immune system effects of CD40, it is well known that the art of drug discovery for autoimmune diseases is highly unpredictable. For example, as drawn to use for patients requiring immunosuppression, Auchincloss (chapter 11 in Transplantation Immunology, Bach and Auchincloss Eds., Wiley-Liss, New York, 1995, pages 211-218) teach that many different strategies have been developed to achieve transplantation tolerance some of which have led to indefinite graft survival in rodents, however, none of these strategies have yet been applied to human patients in a way that allows reliable withdrawal of exogenous immunosuppression. While tolerance inducing strategies have worked well in rodents, such strategies have been much less successful even when tested in nonhuman primates and other large animals (page 211). Further, the conclusion on page 217 states that although more than a dozen different techniques to induce tolerance in rodents are now available, the fact remains that none of them has been used successfully in the clinic. Inducing transplantation tolerance in humans must therefore be very hard to do and that reading of those reading this chapter should be wary of simple solutions to this complex problem. Further, although it is known that

CD40 is involved with autoimmune diabetes and that CD40 blockade prevents autoimmune diabetes (Von Herrath, 2002, abstract, 2nd Annual Meeting of the Fed. Of Clinical Immunological Societies), it is not clear how the identified effective agent would be useful to treat diabetes since it is known in the art that by the time of clinical onset, most of the beta cells in the islets have been destroyed and the blockade of CD40 would not be expected to treat the disease, given the loss of the cells essential for producing insulin. Further, although the specification provides general teachings on effective dose and method of administration (p. 37, lines 12-27) there are no teachings in the specification that establish effective doses for the identified effective agent. It is clear that to function as contemplated, the identified effective agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the site of action, interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition, the target cells must not have an alternate means of survival despite action at the proper site for the identified effective agent. The specification does not provide teachings drawn to the in vivo environment and variables such as biological stability, half-life or clearance from the blood which are important parameters in achieving successful therapy. The identified effective agent may be inactivated in vivo before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the identified effective agent. In addition, the identified effective agent may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues

where the identified effective agent has no effect, circulation into the target area may be insufficient to carry the identified effective agent and a large enough local concentration may not be established. Finally, it is not clear how the identified effective agent would be able to treat the laundry list of immune system diseases because it does not appear that the identified effective agent would be useful to clear autoreactive T or B cells that are already in the system. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one skilled in the art to predict that the identified effective agent will function as contemplated with a reasonable expectation of success in the absence of further experimentation.

Neither the specification nor the art of record teaches whether CAP-1 is sufficient or even necessary for the modulation of CD40 function. Clearly, additional experimentation is required in order to use the effective agents to be identified with the instant method. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as contemplated, that is to identify an effective agent for the treatment of human diseases with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. Claims 19 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth four molecules that bind to CAP-1, that is CD40, CAP-1, TRAF1, TRAF2 and therefore the written description is not commensurate in scope with the claims drawn to a method of identifying an effective agent that alters the association of a CAP-1 with a second molecule.

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are drawn to a method of identifying an effective agent that alters the association of CAP-1 with a second molecule. The specification exemplifies the identification of CAP-1 using a yeast two-hybrid system (see Example I, pages 41-46) wherein it was found that CAP-1 binds to CD40 intracellular domain but not to TNFR2, Fas, Ras, Bcl-2 or Lamin C fusion proteins (see Table I). The specification further exemplifies the production of fusion proteins, GST-CAP-1, GST-CD40, GST-TNFR1, GST-Fas, GST-TNFR2 and their use in an *in vitro* binding assay. No interactions were detected between CAP-1 and GST-fusion proteins containing the cytosolic domains of Fas, TNF-R1, TNF-R2, or Fas. However, interactions were found between GST-CAP-1 and CD40 and CAP-1 (see Example II, pages 47-53, in

particular, page 49, lines 20-25). The specification further states that it is likely that CAP-1 will bind to TRAF1 and TRAF2 because of the structural similarities between the TRAF domains of TRAF1, TRAF2 and CAP-1 (p. 16, lines 5-16).

The instant disclosure of two molecules known to bind CAP-1 and the hypothesized binding of the TRAF1 and TRAF2 species does not adequately describe the scope of the claimed genus, especially in view of the teaching in the specification that CAP-1 does not bind to TNFR2, Fas, Ras, Bcl-2 or Lamin C . The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of identified effective agents. Further, there is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using the yeast two-hybrid system. Although drawn to the DNA arts, the findings in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity, that is in this case, an agent that associates with CAP-1, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or

physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In addition, there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the second molecules encompassed and no identifying characteristic or property of the instant second molecule is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is undefined other than as by CAP-1, CD40 and the putative binding proteins TRAF1 and TRAF2, the disclosure of a these polypeptides and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only a method of identifying an effective agent that alters the association of a CAP-1, with CD40, CAP-1, TRAP-1, TRAP2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

8. In the interests of compact prosecution, if Applicant were to amend the claims to recite the alteration of association of CAP-1 with CAP-1, CD40, TRAF1, TRAF2

and if Applicant were able to overcome the rejections set forth above, Claims 19 and 34 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabled for a method of identifying an effective agent that alters the association of CAP-1 with a second molecule wherein said second molecule is selected from the group consisting of CAP-1 and CD40, does not reasonably provide enablement for said method with a second molecule selected from the group consisting of CAP-1, CD40, TRAF1, TRAF2. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to use the invention commensurate in scope with these claims.

If amended, the claims would be drawn to a method of identifying an effective agent that alters the association of CAP-1 with a second molecule wherein said second molecule is selected from the group consisting of CAP-1, CD40, TRAF1, TRAF2. The specification exemplifies the identification of CAP-1 using a yeast two-hybrid system (see Example I, pages 41-46) wherein it was found that CAP-1 binds to CD40 intracellular domain but not to TNFR2, Fas, Ras, Bcl-2 or Lamin C fusion proteins (see Table I). The specification further exemplifies the production of fusion proteins, GST-CAP-1, GST-CD40, GST-TNFR1, GST-Fas, GST-TNFR2 and their use in an *in vitro* binding assay. No interactions were detected between CAP-1 and GST-fusion proteins containing the cytosolic domains of Fas, TNF-R1, TNF-R2, or Fas. However, interactions were found between GST-CAP-1 and CD40 and CAP-1 (see Example II, pages 47-53, in particular, page 49, lines 20-25). The specification further states that it is likely that CAP-1 will bind to TRAF1 and TRAF2 because of the structural

similarities between the TRAF domains of TRAF1, TRAF2 and CAP-1 (p. 16, lines 5-16). Finally, the specification teaches that CAP-1 has 26% and 30% overall homology to TRAF1 and TRAF2, respectively which have recently been shown to bind to the cytosolic domain of TNFR2. The strongest homology was located in the C-terminal regions of these proteins corresponding to the TRAF domains of TRAF1 and TRAF2. The cytosolic domain of CAP-1 has 57% and 59% amino acid identity to the analogous domains in TRAF1 and TRAF 2 (p. 54, lines 7-23).

One cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because although there is 57% and 59% identity between the TRAF domains of CAP-1 and TRAF1 and TRAF2, respectively, there is clearly a 43% as well as a 41%, respectively difference between CAP-1 and the two TRAFs. Further, there is a 74% and 70%, respectively, difference between the overall homology of TRAF1 , TRAF2 and CAP-1. Although the specification suggests that the two TRAFs would form heteromers with CAP1, it is not clear, given the clear differences in identity why this suggestion has been made since the effects of these dissimilarities on protein structure and function cannot be predicted. Certainly, it is clear that TRAF1, TRAF2 and CAP-1 have different binding specificites. The specification clearly teaches that CAP-1 does not bind to TNFR2. However, Rothe et al, Cell, 1994.78:681-692, IDS item) specifically teach that TRAF1 binds to TNFR2 and that although TRAF2 does not bind to TNFR2, it is associated with TNFR2 through formation of a heterodimer with TRAF1 (see abstract). Further, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message

that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given the know exquisite requirements of protein binding, with a 43% as well

as a 41%, respectively difference between CAP-1 and the two TRAFs in the TRAF domains as well as a 74% and 70%, respectively, difference between the overall homology of TRAF1 , TRAF2 and CAP-1 it could not be predicted, based on sequence similarity with CAP-1, nor would it be expected that either of the two TRAFs would bind to CAP-1. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As

more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 43% as well as a 41%, respectively difference between CAP-1 and the two TRAFs in the TRAF binding domains as well as a 74% and 70%, respectively, difference between the overall homology of TRAF1 , TRAF2 and CAP-1 it could not be predicted, nor would it be expected that either of the two TRAFs would form heteromers with CAP-1 based only on the limited sequence similarity of the three proteins. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that either TRAF1 or TRAF2 would bind to CAP-1 or that a method of identifying an effective agent that alters the association of CAP-1 with a second molecule, wherein that molecule is TRAF1 or TRAF2 will function as claimed with a reasonable expectation of success. For the above reasons, it

appears that undue experimentation would be required to practice the claimed invention.

9. Claims 19 and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 34 are indefinite in the recitation of an "effective agent". The phrase "effective agent" is indefinite when the claims fail to state the function which is to be achieved. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

New Grounds of Objection

10. Claim 19 is objected to because it is missing a step in Section (a). Section (a) recites "contacting CAP-1 with the second molecule under suitable conditions, which allow said Cap-1 and said second molecule to bind with an agent suspected of being able to alter the association of said CAP-1 with a second molecule". The missing step is contacting the complex with the agent suspected of being able to alter the association of said CAP-1 with said second molecule. As currently constituted the claim is only drawn to the binding of CAP-1 with the second molecule in a set of conditions, but does not require the addition of a candidate effective agent.

11. No claims allowed.

12. All other objections and rejections recited in Paper No. 12 are withdrawn.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703)

305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 29, 2003